IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant: Monty Krieger

Serial No.: 09/148,012 Art Unit: 1647

Filed: September 4, 1998 Examiner: Robert S. Landsman

For: *SR-BI ANTAGONIST AND USE THEREOF AS CONTRACEPTIVES AND IN THE TREATMENT OF STEROIDAL OVERPRODUCTION*

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY BRIEF

Sir:

This is a Brief in reply to the Examiner's Answer mailed December 18, 2003 in the above-identified patent application. A Request for Oral Hearing accompanies this Answer along with the appropriate fee. It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-1868.

(2) RELATED APPEALS AND INTERFERENCES

On page 2 of the appeal brief filed September 19, 2003 under the section entitled "(2) RELATED APPEALS AND INTERFERENCES" it is expressly stated that there are no related appeals or interferences known to appellant, the undersigned, or appellant's assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal.

(8) ARGUMENTS

Response to Examiner's Arguments

Appellant maintains that the invention is a pioneering invention - the discovery that abnormal levels of lipoproteins and/or cholesterol levels can negatively affect fertility, and that altering lipoprotein and/or cholesterol levels can affect a female's ability to reproduce. The Appellant has developed a method to alter a female's ability to reproduce by altering serum levels of lipoproteins, LDL, HDL and/or cholesterol. This method has applications for contraception as well as in treating fertility disorders. The example in the application uses an acceptable animal model for control of fertility in humans – the mouse, to demonstrate that administration of a drug known to control cholesterol in humans can be used to restore fertility in the females, allowing animals to conceive and carry to full term babies, as compared to the controls that were completely unable to do so. Measurements of the lipoproteins and cholesterol show much more normalized levels in those animals in whom fertility was restored. The mechanism of action is still not completely clear, but it is important to note that it was a drug already approved for use in humans to lower cholesterol that was used in an animal model that is commonly used to screen drugs for human use.

(i) Rejections Under 35 U.S.C. § 112, first paragraph (written description)

The Examiner is confused by the mechanism of SR-BI action described in the Appeal Brief. To clarify the mechanism of SRBI action, a decrease in SRBI causes an increase in cholesterol levels. On page 5, paragraph 3 of the Appeal Brief, the sentence should read "that

decreasing levels of SR-BI activity *increases* cholesterol levels and alters lipoprotein levels;". Page 12 of the specification states that SR-BI is a scavenger receptor protein that transports cholesterol from the blood into tissues such as liver and steroidogenic tissues thus decreasing plasma levels of cholesterol. In situations where SRBI expression is reduced or SRBI function is blocked (as in a knockout mouse), plasma cholesterol levels increase.

The claims are directed to a method "to alter fertility or treat a reproductive disorder". One of skill in the art would comprehend that the term "alter" indicates that fertility can be either reduced or enhanced. Fertility reductions would be desirable for methods of contraception as described on page 13, lines 8-15 of the specification, and Example 6. Enhancement of fertility would be desirable for situations where a fertility disorder prevents reproduction. Example 5 demonstrates that enhancement of SRBI function reduces plasma cholesterol levels. Claims 2, 4 and 5 are directed to altering SRBI expression to reduce or enhance fertility. Claims 3, 6 and 7 are directed to altering SRBI binding to reduce or enhance fertility. The specification makes it very clear in which direction SR-BI must be altered to alter fertility or treat a reproductive disorder. There is no ambiguity. The method principles and steps are adequately described by the specification in view of the knowledge in the art.

(ii) Rejections Under 35 U.S.C. § 112, first paragraph (enablement)

As described above, the claims are directed to modulating fertility by increasing or decreasing the activity of SR-BI. The claims are enabled because the Appellant has described specifically which direction one would need to alter cholesterol and lipoprotein levels in order to increase or decrease fertility. The Appellant has established a connection between cholesterol

and lipoprotein levels and fertility. The Appellant has provided an example (although none are required) to show a decrease in fertility after inhibiting SR-BI function and increasing serum cholesterol levels. The Appellant has submitted an article by Miettinen et al. to demonstrate that using the same methods and concepts taught by the specification, fertility can be restored.

The Examiner asserts that there is no evidence that women taking cholesterol-lowering drugs exhibit fertility problems. First, it should be noted that there are many causes of infertility. Appellant is not claiming a method of treatment of all types of infertility. Second, cholesterol-lowering drugs are not recommended for administration to women who may be pregnant or trying to become pregnant. (See attached article – there is a definite risk to the fetus from taking cholesterol lowering drugs based on this information). High cholesterol is a problem that develops in women during and following menopause, when estrogen levels decrease significantly. (See attached article)

The role of serum cholesterol levels on fertility is described on page 50 of the specification. The infertile SR-BI knockout mice have extremely elevated cholesterol levels and totally abnormal lipoprotein levels. By decreasing serum cholesterol levels and normalizing lipoprotein levels, one can enhance fertility.

(iii) Rejections Under 35 U.S.C. § 112, second paragraph

The claims are definite and include all necessary steps to practice the claimed method. The treatment regimen is already defined in the claim where the term "an effective amount" is administered. One of skill in the art would understand this "amount" in view of the teachings on

pages 26 and 27 of the specification and knowledge in the art of dose titration and the use of animal models.

The term " to enhance" fertility relates to the process of implantation and development of the embryo. This is described on page 8, lines 8-9 of the specification, where studies demonstrate that infertile females do not produce viable eggs and have a defect involving implantation of the fertilized egg. "Enhancement" refers to an improvement in the viability of the eggs or the ability of a fertilized egg to implant in the uterine wall. One of skill in the art would understand that fertility is a physiological state where the conditions are optimum for initial fertilization, implantation and growth of an embryo. This is why the term "enhanced" is more appropriate than "restored" because a certain threshold of these conditions is required for fertility. One of skill in the art would understand that an improvement in these conditions would constitute an enhancement of fertility. Similarly anything that compromises these conditions would constitute a reduction of fertility.

(9) SUMMARY AND CONCLUSION

For the foregoing reasons, Appellant submits that the claims 1-10, 12, 15, 16 and 20-22 are patentable.

Respectfully submitted,

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Date: February 18, 2004

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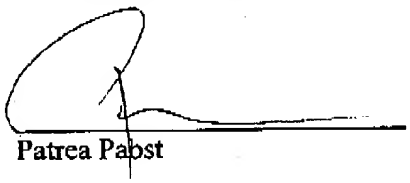
I hereby certify that this Request for Oral Hearing, Reply Brief, and any documents referred to as attached therein are being facsimile transmitted on this date, February 18, 2004, to Mail Stop Appeal Brief-Patents, Commissioner for Patents, Alexandria, VA 22313-1450.



Patrea Pabst

Date: February 18, 2004

June 200

Canadian Family Physician

CLINICAL CHALLENGE

MOTHERISK UPDATE

Use of lipid-lowering agents (statins) during pregnancy

Akiko Hosokawa, MD Benjamin Bar-Oz, MD Shinya Ito, MD

ABSTRACT

QUESTION A 34-year-old patient of mine is taking a "statin" for hyperlipidemia. She is planning pregnancy and is worried about the safety of the drug. How should I advise her?
ANSWER Limited evidence from animal and human studies indicates that statins should no be taken during pregnancy. If a patient is inadvertently exposed during pregnancy, howeve termination does not appear to be medically indicated.

RÉSUMÉ

QUESTION Une de mes patientes prend des « statines » contre l'hyperlipidémie. Elle planif une grossesse et s'inquiète à propos de la sécurité de ce médicament. Comment puis-je la conseiller?
RÉPONSE Des données scientifiques limitées, tirées d'études chez les animaux et les humains, indiquent que les statines ne devraient pas être prises durant la grossesse. Si une patiente était exposée à ce médicament par inadvertance pendant qu'elle est enceinte, il n'e cependant pas indiqué sur le plan médical de mettre un terme à la grossesse.

"Statins," ß-hydroxy-ß-methyglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, have be widely used for treatment of hyperlipidemia and for reducing morbidity and mortality coronary artery disease (CAD).[1-5] Current recommendations suggest discontinuing t medication before conception,[6] especially since stopping therapy for the relatively sh duration of pregnancy is believed to have little effect on long-term outcome.[7] If a patie becomes pregnant while taking the medication, there are no clear guidelines to follow.

Pharmacology of HMG-CoA reductase inhibitors

The HMG-CoA reductase inhibitors currently marketed for clinical use include atorvastat fluvastatin, lovastatin, pravastatin, and simvastatin (cerivastatin was withdrawn from t market because of reports of fatal rhabdomyolysis; it will not be discussed further). The medications reduce the intracellular concentration of cholesterol and result in an increase the activity of low-density lipoprotein cholesterol (LDL-c) receptors that enhances the upta

and catabolism of LDL-c.[8] Clinical trials have shown that all the statins significantly impro various lipid parameters including LDL-c, high-density lipoprotein cholesterol, a triglycerides.[9,10] More importantly, summarized results of both angiographic and clinical tri have shown that aggressively lowering LDL-c by at least 25% with statin therapy can de progression of CAD and decrease the incidence of nonfatal myocardial infarction and dea from CAD.[9,11]

Effects of maternal hypercholesterolemia on a fetus

A growing body of evidence suggests that maternal hypercholesterolemia is associated w development of fetal atherosclerosis. Napoli et al[12] found that fetal aortas fr hypercholesterolemic mothers (mean plasma cholesterol 292 mg/dL before pregnancy a 385 mg/dL during pregnancy) contain a significantly higher number of fatty streak lesions a are larger than fetal aortas from mothers with normal cholesterol levels (total plasi cholesterol < 185 to 200 mg/dL, depending on age).

This difference was even found for mothers who were hypercholesterolemic only duri pregnancy. The authors also discovered that the lesions got significantly larger w advancing age beyond 1 year and that the rate of progression was faster in children hypercholesterolemic mothers. The difference in the rate could not be attributed to t children's cholesterol levels because they were found to be normal. The findings of the studies have been confirmed in animal models.[13,14]

Interventions to reduce cholesterol and lipid oxidation, including cholestyramine and vitamir therapy, significantly reduce lesions at birth.[14,15] These findings suggest the importance maternal cholesterol levels in the pathogenesis of atherosclerosis in children, but their clini importance is still unknown.

Fetal toxicity associated with statins

Atorvastatin (Lipitor). No teratogenic effects of atorvastatin were seen in rats and rabbi even at maternally toxic doses, although fetal body weight was lower than normal.[15] Anott study in rats showed that atorvastatin at maternally toxic doses resulted in a 45% lov survival rate of the offspring, decreased body weight, and abnormal neonatal development.

No data on human pregnancies have been published. We located eight cases in our Mother database of statin use during the first trimester of pregnancy. Among these cases, there we two spontaneous abortions, one premature neonatal death (at 24 weeks' gestation), o elective abortion, two normal outcomes, and two patients lost to follow up. Given the limit information available, atorvastatin should be avoided during pregnancy.

Fluvastatin (Lescol). Manufacturer's data showed no evidence of teratogenicity in rats rabbits given high doses of fluvastatin. The same researchers showed, however, that hi doses of fluvastatin resulted in maternal mortality secondary to cardiomyopathy, weight lo decreased neonatal weight gain, and an increased incidence of stillbirths and neona deaths.[17,18]

Sandoz Pharmaceuticals (manufacturer of Lescol) reported on five human pregnancies There were two normal outcomes, one ectopic pregnancy, one spontaneous abortion, a one unknown outcome. Duration and timing of drug exposure were not mentioned. additional report described a 28-year-old woman taking medications, including fluvasta during her first trimester, who delivered a normal, full-term, healthy infant. Given t evidence to date (ie, maternal mortality in animal models), however, fluvastatin should avoided during pregnancy.

Lovastatin (eg, Mevacor). Administration of lovastatin to pregnant rats at doses of 8 mg/kg daily resulted in decreased maternal weight gain, fetal skeletal malformatic (including vertebrae and ribs), and gastroschisis.[19] No drug-induced changes were seen

rabbits or mice given lovastatin at doses nine to 50 times the maximum recommended dc for humans.[20]

A postmarketing surveillance study[7] reported on 48 cases with known outcome of wom using lovastatin during pregnancy. There were three (6.3%) spontaneous abortions, o (2.1%) stillbirth, four (8.3%) infants with congenital anomalies (atrial or ventricular sep defects, cerebral dysfunction, VATER complex, spina bifida, and holoprosencephaly), (81.2%) normal outcomes, and one case of pedal edema. Based on the timing of expos and diversity of malformations, there is likely no causal relationship between taking the dr and congenital anomalies.[7]

Pravastatin (Pravachol). High doses of pravastatin administered to rats and rabbits had teratogenic effects.[21,22] No data on human use of pravastatin during pregnancy have be published. The manufacturer, Bristol-Myers Squibb, has, however, received 26 case reports exposure during pregnancy. Among these, 11 were exposed during the first trimester, and had normal pregnancy outcomes (personal communication from Bristol-Myers Squibb Canac November 12, 1996). Animal data and known human exposures indicate that pravastatin dc not increase the risk of major congenital anomalies.

Simvastatin (Zocor). Animal studies using both rats and rabbits demonstrated teratogenic effect of high doses of simvastatin.[23,24] Toxic doses, however, resulted maternal weight loss and an increased resorption rate in rabbits.[25] In contrast, high dos resulted in decreased mean fetal body weight and maternal weight gain in rats.[25] Postmarketing surveillance data are available on 86 cases with known pregnancy outcor following exposure to simvastatin.[7] Among these cases, there were 13 (15.1%) spontanec abortions, one (1.2%) fetal death, five (5.8%) congenital anomalies (polydactyly, unilate cleft lip, balanic hypospadia, trisomy 18, and clubfoot), three (3.5%) miscellaneous adve outcomes possibly related to prematurity, and 64 (74%) normal outcomes. Based on anin and human data, exposure to simvastatin during pregnancy does not appear to increase t risk of congenital malformations.

Conclusion

Results of animal studies indicate that many statins are associated with adverse fe outcomes at maternally toxic doses. The limited human data suggest that statins are r major human teratogens.[7] Thus, if women are inadvertently exposed to statins befc recognition of pregnancy, they can be reassured that their fetuses do not appear to be increased risk.

Nonetheless, it seems reasonable to follow the current recommendation of discontinuing t medication immediately upon recognition of pregnancy or before conception if pregnancy planned.[6,19,21,27,28] With new evidence to suggest that maternal hypercholesterolemia has detrimental effect on a developing fetus, this recommendation might change, particularly results of further studies of statins and other agents, such as vitamin E, during pregnar become available.

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Motherisk questions are prepared by the Motherisk Team at the Hospital for Sick Children Toronto, Ont. **Drs Bar-Oz** and **Ito** are members of the Motherisk Program. **Dr Hosokawa** a resident in the family medicine program at the University of Toronto.

Do you have questions about the safety of drugs, chemicals, radiation, or infections i women who are pregnant or breastfeeding? We invite you to submit them to the Motheris Program by fax at (416) 813-7562; they will be addressed in future Motherisk Update Published Motherisk Updates are available on the College of Family Physicians of Canac website (www.cfpc.ca). Some articles are published in The Motherisk Newsletter and c the Motherisk website (www.motherisk.org) also.

What Are Healthy Levels of Cholesterol?

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What Are Healthy Levels of Cholesterol?

Your total blood cholesterol level
Your total blood cholesterol will fall into one of these categories:

Desirable — Less than 200 mg/dL
Borderline high risk — 200-239 mg/dL
High risk — 240 mg/dL and over

Here is some more explanation about each of these categories.

Desirable
If your total cholesterol is less than 200 mg/dL, your heart attack risk is relatively low, unless you have other risk factors. Even with a low risk, it's still smart to eat foods low in saturated fat and cholesterol, and also get plenty of physical activity. Have your cholesterol levels measured every five years — or more often if you're a man over 45 or a woman over 55.

Borderline high risk
People whose cholesterol level is from 200 to 239 mg/dL are borderline high risk. About a third of American adults are in this (borderline) group; almost half of adults have total cholesterol levels below 200 mg/dL.

Have your cholesterol and HDL rechecked in one to two years if:

- Your total cholesterol is in this range
- Your HDL is less than 40 mg/dL
- You don't have other risk factors for heart disease

You should also lower your intake of foods high in saturated fat and cholesterol to reduce your blood cholesterol level to below 200 mg/dL. Your doctor may order another blood test to measure your LDL cholesterol. Ask your doctor to discuss your LDL cholesterol with you. Even if your total cholesterol is between 200 and 239 mg/dL, you may not be at high risk for a heart attack. Some people — such as women before menopause and young, active men who have no other risk factors — may have high HDL cholesterol and desirable LDL levels. Ask your doctor to interpret your results. Everyone's case is different.

High risk
If your total cholesterol level is **240 or more**, it's definitely high. Your risk of heart attack and stroke is greater. In general, people who have a total cholesterol level of 240 mg/dL have twice the risk of heart attack as people whose cholesterol level is 200 mg/dL.

You need more tests. Ask your doctor for advice. About 20 percent of the U.S. population has high blood cholesterol levels.

Your LDL cholesterol level
Your LDL cholesterol level greatly affects your risk of heart attack and stroke. The lower your LDL cholesterol, the lower your risk. In fact, it's

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a better gauge of risk than total blood cholesterol. Your LDL cholesterol will fall into one of these categories:

LDL Cholesterol Levels	
Less than 100 mg/dL	Optimal
100 to 129 mg/dL	Near Optimal/ Above Optimal
130 to 159 mg/dL	Borderline High
160 to 189 mg/dL	High
190 mg/dL and above	Very High

The key point to remember is, the lower your LDL cholesterol, the lower your risk. Your doctor may prescribe a diet low in saturated fat and cholesterol, regular exercise and a weight management program if you're overweight. If you can't lower your cholesterol with these efforts, medications may also be prescribed to lower your LDL cholesterol. Check these categories and the goals for treatment that can lower your risk of heart attack.

LDL level at which to consider drug therapy

	LDL Level	Goal
People without coronary heart disease and with fewer than two risk factors	190 mg/dL or higher*	160 mg/dL or lower
People without coronary heart disease and with two or more risk factors	160 mg/dL or higher	130 mg/dL or lower
People with coronary heart disease	130 mg/dL or higher**	100 mg/dL or lower

**In men less than age 35 and premenopausal women with LDL cholesterol levels of 190 to 219 mg/dL, drug therapy should be delayed except in high-risk patients such as those with diabetes.*

***In coronary heart disease patients with LDL cholesterol levels of 100 to 129 mg/dL, the doctor should consider whether to initiate drug treatment in addition to the American Heart Association Therapeutic Lifestyle Changes (TLC) diet.*

If you don't know if you have other risk factors for heart disease, check out the American Heart Association's list by clicking here.

Your HDL cholesterol level
In the average man, HDL cholesterol levels range from 40 to 50 mg/dL. In the average woman, they range from 50 to 60 mg/dL. HDL cholesterol that's less than 40 mg/dL is low. Low HDL cholesterol puts you at high risk for heart disease. Smoking, being overweight and being sedentary can all result in lower HDL cholesterol. If you have low HDL cholesterol, you can help raise it by:

- Not smoking
- Losing weight (or maintaining a healthy weight)

- Being physically active for at least 30–60 minutes a day on most or all days of the week

People with high blood triglycerides usually have lower HDL cholesterol and a higher risk of heart attack and stroke. Progesterone, anabolic steroids and male sex hormones (testosterone) also lower HDL cholesterol levels. Female sex hormones raise HDL cholesterol levels.

Cholesterol ratio
Total blood cholesterol is the most common measurement of blood cholesterol. It's the number you normally receive as test results. Cholesterol is measured in milligrams per deciliter of blood (mg/dL). Knowing your total blood cholesterol level is an important first step in determining your risk for heart disease. However, a critical second step is knowing your HDL or "good" cholesterol level.

Some physicians and cholesterol technicians use the ratio of total cholesterol to HDL cholesterol in place of the total blood cholesterol. The American Heart Association recommends that the absolute numbers for total blood cholesterol and HDL cholesterol levels be used. They're more useful to the physician than the cholesterol ratio in determining the appropriate treatment for patients.

The ratio is obtained by dividing the HDL cholesterol level into the total cholesterol. For example, if a person has a total cholesterol of 200 mg/dL and an HDL cholesterol level of 50 mg/dL, the ratio would be stated as 4:1. The goal is to keep the ratio below 5:1; the optimum ratio is 3.5:1.

Your triglyceride level
Your triglyceride level will fall into one of these categories:

Triglyceride Level	Classification
Less than 150 mg/dL	Normal
150-199 mg/dL	Borderline-high
200-499 mg/dL	High
500 mg/dL or higher	Very high

Many people with high triglycerides have underlying diseases or genetic disorders. If this is true for you, the main therapy is to change your lifestyle. This includes controlling your weight, eating foods low in saturated fat and cholesterol, exercising regularly, not smoking and, in some cases, drinking less alcohol. People with high triglycerides may also need to limit their intake of carbohydrates to no more than 45–50 percent of total calories. The reason for this is that carbohydrates raise triglycerides in some people and lower HDL cholesterol. Use products with monounsaturated and polyunsaturated fats.